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Palladium-Catalyzed Multiple Arylation of Thiophenes

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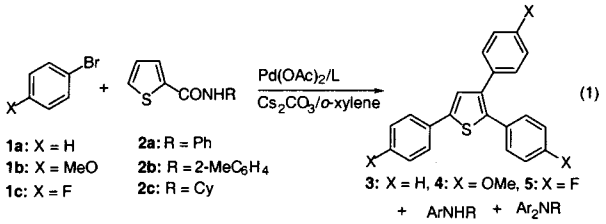
Palladium-catalyzed aryl−aryl coupling is now widely used for preparing various biologically active compounds and organic functional materials having biaryl skeletons.[1−3] The reaction is usually carried out with aryl halides and arylmetals. It is also known that the direct intermolecular arylation of appropriately functionalized aromatic compounds[4] and five-membered heteroaromatics[4,5] can regioselectively occur via C−H cleavage. We recently reported that aromatic substrates such as phenols, aryl ketones, and benzyl alcohols undergo direct multiple (two to five times) arylation on treatment with excess aryl halides in the presence of palladium catalysts to give the corresponding oligoaryl compounds.[6] As part of our study of the catalytic multisubstitution of aromatics,[6,7] we have examined the reaction of thiophenes,[8] since poly- and oligoaryl compounds involving a thiophene unit have recently attracted much attention as the organic components of electronic devices.[9] Consequently, it has been found that certain monosubstituted thiophenes can effectively undergo unprecedented 2,3(or 4),5-triarylation as well as 2,5- and 3,5-diarylation, which is reported herein.

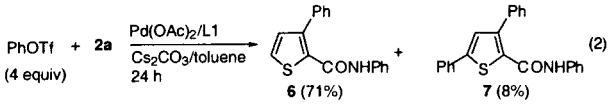
The triarylation found first is shown in eq 1 with 2-thiophenecarboxamides as substrates, in which an unusual formal decarbamoylation via C−C cleavage is involved. In a typical experiment,



(1)

N-(2-thenoyl)aniline (**2a**) (1 mmol) with bromobenzene (**1a**) (6 mmol) in the presence of $Pd(OAc)_2$ (0.1 mmol), P(*o*-biphenyl)-(*t*-Bu)$_2$ (L1) (0.2 mmol), and Cs_2CO_3 (6 mmol) in refluxing *o*-xylene for 18 h gave 2,3,5-triphenylthiophene (**3a**) in 96% yield (83% after purification) (entry 1 in Table 1). Triphenylamine (82%) was detected as the product derived from the carbamoyl moiety. This indicates that aniline liberated from the substituent was also diphenylated. P(*t*-Bu)$_3$ (L2) could be used in place of the Buchwald's ligand (L1), while it was somewhat less effective (entry 2).[10,11] The reactions of **2a** with 4-methoxy- and 4-fluorobenzenes (**1b** and **1c**) similarly proceeded to give the corresponding 2,3,5-triarylthiophenes (**4** and **5**), in good yields (entries 3 and 4). *N*-(2-Thenoyl)-2-methylaniline (**2b**) reacted with **1a** (4 equiv) to give **3** in 83% yield. In this case, *N*-(2-methylphenyl)aniline was produced as the major byproduct, indicating that in the triarylthiophene preparation, the amount of **1** can be reduced by using the amide **2b** (entry 5). The reaction of *N*-(2-thenoyl)cyclohexylamine (**2c**) with **1a** also gave **3** (entry 6), although it was less efficient.

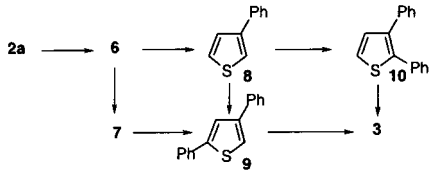
The following experimental results seem to be informative in considering the reaction sequence of this unique thiophene triarylation. (a) The reaction of **2a** with phenyl triflate in toluene at 110 °C for 24 h gave 3-monophenylated and 3,5-diphenylated products, **6** and **7**, in 71% and 8% yields, respectively (eq 2), while that with



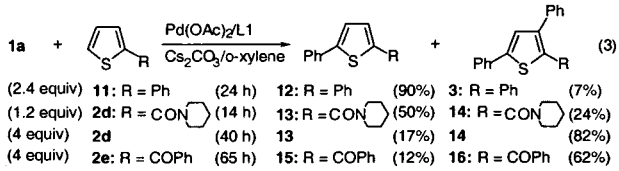
(2)

1a was sluggish under the conditions. (b) Analysis of the reaction mixture with **1a** in refluxing *o*-xylene at 4 h confirmed the formation of **6** (17%), **7** (7%), 3-phenylthiophene (**8**) (19%), 2,4-diphenylthiophene (**9**) (21%), 2,3-diphenylthiophene (**10**) (10%), and **3** (4%) along with aniline (20%) and diphenylamine (10%) (Scheme 1).

Scheme 1



Thus, **2a** appears to be phenylated successively at the 3- and 5-positons to give **6** and **7**. Then, both the compounds undergo decarbamoylation to give **8** and **9**, which are further di- and monophenylated, respectively, to give **3**. It was confirmed that **8** was quantitatively diphenylated under the present conditions to give **3** (vide infra). However, the reaction of 2-phenylthiophene (**11**) with **1a** gave 2,5-diphenylthiophene (**12**) as the predominant product along with only a minor amount of **3** (eq 3). Thus, the route via **11** and **12** does not seem to participate in the reaction.



(3)

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Table 1. Reaction of *N*-(2-Thenoyl)amines with Bromobenzenes[a]

				products, % yield[b]		
entry	bromide	amide	time (h)	thiophene	ArNHR	Ar_2NR
1	**1a**	**2a**	18	**3**, 96 (83)	−[c]	82
2[d]	**1a**	**2a**	24	**3**, 84	−	83
3	**1b**	**2a**	24	**4**, 73 (68)	−	97
4	**1c**	**2a**	24	**5**, 77 (71)	19	64
5[e]	**1a**	**2b**	18	**3**, 83	73	4
6	**1a**	**2c**	20	**3**, 52	−	−

[a] Reaction conditions: [**1**]:[**2**]:[$Pd(OAc)_2$]:[L = L1]:[Cs_2CO_3] = 6:1:0.1:0.2:6 (in mmol), in refluxing *o*-xylene under N_2. [b] Determined by GLC. The value in parentheses is isolated yield. [c] Not detected or negligible. [d] L = L2. [e] [**1a**]:[Cs_2CO_3] = 4:4 (in mmol).

Table 2. Reaction of 3-Substituted Thiophenes with Bromobenzenes[a]

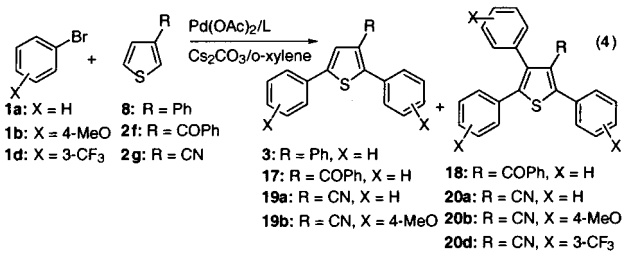
entry	bromide (mmol)	thiophene	time (h)	products, % yield[b] di[c]	tri[d]
1	**1a** (2.4)	**8**	24	**3**, 97 (88)	– [e]
2	**1a** (4)	**2f**	18	**17**, 86 (80)	**18**, 10
3	**1a** (4)	**2f**	72	**17**, 44	**18**, 33
4	**1a** (2.4)	**2g**	36	**19a**, 96 (83)	–
5	**1a** (6)	**2g**	70	**19a**, 4	**20a**, 76 (65)
6[f]	**1a** (6)	**2g**	72	**19a**, 90	**20a**, 7
7	**1b** (2.4)	**2g**	48	**19b**, 92 (80)	–
8	**1b** (6)	**2g**	140	**19b**, 28	**20b**, 48
9	**1d** (6)	**2g**	52	–	**20d**, 78 (72)

[a] Reaction conditions: [thiophene]:[$Pd(OAc)_2$]:[L = L1] = 1:0.1:0.2 (in mmol), [**1**] = [Cs_2CO_3], in refluxing *o*-xylene under N_2. [b] Determined by GLC. The value in parentheses is isolated yield. [c] Diarylated product. [d] Triarylated product. [e] Not detected or negligible. [f] L = L2.

To obtain some insight into the mode of decarbamoylation in Scheme 1,[12] diphenylated amide **7** (0.2 mmol) was heated in the presence of $Pd(OAc)_2$ (0.02 mmol), L1 (0.04 mmol), and Cs_2CO_3 (1 mmol) in *o*-xylene for 24 h. The amide disappeared to produce **9** quantitatively together with aniline. No reaction occurred with use of $Pd(dba)_2$ in place of $Pd(OAc)_2$ ($Pd(dba)_2$ could be used in the arylation of **2a**) or in the absence of any palladium species or base. On the basis of these results, it is reasonable to consider that the process involves Pd(II)-catalyzed and base-promoted hydrolytic C−N fission, followed by decarboxylative C−C cleavage,[13] though further studies are required to establish the detailed mechanism.

In contrast to the results with **2a**−**c**, treatment of *N*-(2-thenoyl)-piperidine (**2d**) with **1a** gave corresponding 5-monophenylated and 3,5-diphenylated compounds, **13** and **14**, and tertiary amide products resisted C−C cleavage (eq 3). It is worth noting that initial phenylation of **2a** takes place preferably at the 3-position, followed by the second phenylation at the 5-position, whereas the reaction of **2d** occurs in the reverse order. This sharp contrast leads us to deduce that 3-arylation of **2a** proceeds by a coordination assisted mechanism,[6c] while that of **2d** occurs either via carbopalladation or electrophilically.[14] The 5-phenylation may proceed electrophilically in both reactions.[8b] As expected, the reaction of 2-benzoylthiophene (**2e**) with **1a** proceeded in a manner similar to that of **2d** (eq 3).

As described above, 3-phenylthiophene (**8**) was efficiently diphenylated at the 2- and 5-positions (eq 4 and entry 1 in Table 2). Similarly, the reaction of 3-benzoylthiophene (**2f**) with **1a** (4 equiv) for 18 h gave 3-benzoyl-2,5-diphenylthiophene (**17**) in 86% yield (entry 2). Interestingly, a small, but meaningful amount of triphenylated compound (**18**) (10%) was formed in this reaction, this being the second example of thiophene triarylation. The yield of **18** was increased up to 33% by prolonging the reaction time (entry 3). 3-Cyanothiophene (**2g**) was found to be effectively triphenylated to afford 3-cyano-2,4,5-triphenylthiophene (**20a**) as the predominant product (entry 5), while selective 2,5-diarylation of the substrate was achieved by using a limited amount of **1a** (entry 4). These results indicate that an electron-withdrawing group at the 3-position, which may increase the acidity of 4-hydrogen, enables the triarylation.[8b] It is noted that the reaction of **2g** with L2 as ligand could give only a small amount of **20a** (entry 6), showing that the identity of ligands significantly affects the multiple arylation. The reaction of **2g** was also found to be influenced by the substituent of bromobenzene (entries 8 and 9). Thus, triarylation with **1d** (X = 3-CF_3) proceeded smoothly, whereas that with **1b** (X = 4-OMe) was relatively slow. This suggests that the reaction at the 4-position is enhanced by increasing the electrophilic character of arylpalladium(II) species.



In summary, we have reported that secondary 2-thiophenecarboxamides efficiently undergo unique triarylation accompanied by formal decarbamoylation under palladium catalysis. 3-Substituted thiophenes, especially having an electron-withdrawing group, are also triarylated, while selective diarylation of them can be performed. The present method appears to be useful for preparing various oligoaryl compounds having a thiophene unit.

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Supporting Information Available: Standard experimental procedure and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We previously reported that CuI is an effective promoter for the Pd-catalyzed 2- or 5-arylation of thiophenes and thiazoles in DMF,[8b] but no positive effect of it was observed in the present conditions.
(12) Since no decarbamoylation was observed in the arylation of benzanilide,[6c] the cleavage appears to be characteristic in the heterocyclic system.
(13) It was confirmed that 3-phenylbenzo[*b*]thiophene-2-carboxylic acid as a model intermediate underwent decarboxylative phenylation effectively under the present conditions, which supports the consideration. The hydroxyl source for the C−N fission may be bicarbonate formed during the reaction or adventitious water. Another possible mode of the decarbamoylation is that yielding phenylisocyanate. Although participation of the route cannot be excluded, no evidence for generation of the isocyanate, such as detection of diphenylurea, was obtained.
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